SYNOPSIS

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| Name of Sponsor/Company | Daiichi Sankyo Co., Ltd. |
| Name of Finished Product | NARUSUS® TABLETS |
| Name of Active Ingredient | hydromorphone hydrochloride (INN) |
| Title of Study | DS-7113b extended-release (ER) tablet phase III study<br>A randomized double-blind comparison study with extended-release oxycodone in opioid-naive patients with cancer pain |
| Investigators | - |
| Study Centre(s) | 49 sites |
| Publication (reference) | J Pain Res. 2017 Aug 18;10:1953-1962<br>A randomized, double-blind study of hydromorphone hydrochloride extended-release tablets versus oxycodone hydrochloride extended-release tablets for cancer pain: efficacy and safety in Japanese cancer patients (EXHEAL: a Phase III study of EXtended-release HydromorphonE for cAncer pain reLief) |
| Studied Period | October 2014 – September 2015 |
| Phase of Development | Phase 3 |
| Objectives | To evaluate the efficacy and safety of DS-7113b ER tablet additionally dosed in a randomized double-blind comparison study with ER oxycodone in opioid-naive patients under cancer pain management refractory to non-opioid analgesics. |
| Methodology | A multicenter, active controlled, randomized, double-blind, parallel-group study |
| Number of Patients (planned and analyzed) | Planned:180 subjects<br>Analyzed: 178 subjects |
| Diagnosis and Main Criteria for Inclusion | Inclusion:<br>・ Patients receiving non-opioid analgesics for cancer pain, who have not been receiving opioid analgesics<br>・ Patients whose VAS is ≥ 35 mm and judged necessary to be treated with strong opioid analgesics<br>・ Patients with an ECOG Performance Status (PS) is ≤ 3, etc.<br>Exclusion:<br>・ Patients with serious hepatic, renal, or respiratory disorder.<br>・ Patients with symptom(s)/finding(s) falling under the |

<table>
<tr><td></td><td>contraindications or relative contraindications stated in the package insert for oxycodone hydrochloride powder and morphine hydrochloride preparations, etc.</td></tr>
<tr><td>Test Product, Dose and Mode of Administration, Batch Number</td><td>Test product (batch number):<br>DS-7113b ER tablet 2 mg（D7113T2H14M01 ）<br>DS-7113b ER tablet 6 mg（D7113T2H14M03 ）<br>DS-7113b ER tablet 12 mg（D7113T2H14M05 ）<br>DS-7113b ER tablet 24 mg（D7113T2H14M07 ）<br>Dosage and Administration:<br>As in the table below, subjects received a hydromorphone ER tablet or a placebo tablet orally once daily for 7 days. The initial doses of hydromorphone hydrochloride was 4 mg/day. When it was judged that a dose increase or reduce was necessary during the period of study drug administration, it was possible to increase or reduce the dose step by step.
<table>
<tr><th></th><th>Daily dose</th></tr>
<tr><td>1</td><td>4 mg</td></tr>
<tr><td>2</td><td>8 mg</td></tr>
<tr><td>3</td><td>8 mg</td></tr>
<tr><td>4</td><td>12 mg</td></tr>
<tr><td>5</td><td>16 mg</td></tr>
<tr><td>6</td><td>24 mg</td></tr>
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<tr><td>Duration of Treatment</td><td>Treatment period: 7 days<br>Post-treatment observation period: 1 day</td></tr>
<tr><td>Reference Therapy, Dose and Mode of Administration, Batch Number</td><td>Reference Therapy (batch number):<br>Oxycodone hydrochloride ER tablet 5 mg（3462）<br>Oxycodone hydrochloride ER tablet 10 mg（3456）<br>Oxycodone hydrochloride ER tablet 20 mg（3435）<br>Dosage and Administration:<br>As in the table below, subjects received oxycodone hydrochloride ER tablet or placebo tablet orally once daily for 7 days. The initial doses of oxycodone hydrochloride was 10 mg/day. When it was judged that a dose increase or reduce was necessary during the period of study drug administration, it was possible to increase or reduce the dose step by step.
<table>
<tr><th></th><th>Daily dose</th></tr>
<tr><td>1</td><td>10 mg</td></tr>
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| | 2 20 mg<br>3 40 mg<br>4 60 mg<br>5 60 mg<br>6 80 mg |
| Criteria for Evaluation | Efficacy: Change of VAS between pre-treatment and end of treatment (Primary endpoint)<br>Safety: Adverse event, Clinical laboratory evaluation |
| Statistical Method | Primary endpoint:<br>Summary statistics were calculated for VAS scores at baseline, at treatment completion/discontinuation and for the change in VAS scores. Analysis of covariance (ANCOVA) was conducted using the baseline VAS scores as a covariate to calculate the 95% CI (two-sided) for a difference in the least squares mean in the magnitude of change in VAS scores between the hydromorphone and oxycodone groups VAS score, and ensured that the upper limit did not exceed 10 mm, which was defined as the non-inferiority limit. *P*-values and least squares means for each group were calculated. |
| Summary - Conclusion | ・ The intergroup difference (95% CI) in the least squares mean for the change in VAS scores at completion/discontinuation of treatment was −0.4 mm (−5.9 to 5.0 mm). Given that the upper limit of the 95% CI was <10 mm, the non-inferiority limit determined at the time of planning. Therefore, the non-inferiority of hydromorphone relative to oxycodone was suggested.<br>・ The incidence of adverse events was 80.7% in the hydromorphone group and 83.7% in the oxycodone group, and no significant intergroup difference was observed. However the incidence rates of nausea and vomiting were higher in the hydromorphone group than in the oxycodone group, tthe severity of nausea and vomiting was mild or moderate in all these patients and approximately 70% was mild of these patients. No significant intergroup differences of the incidence of serious adverse event, severe adverse event and adverse event leading to discontinuation of study treatment were observed. |

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| | Therefore, the efficacy and safety of hydromorphone ER tablets are comparable to those of oxycodone ER tablets formulation. |
| Date of Report | March 26, 2018 |